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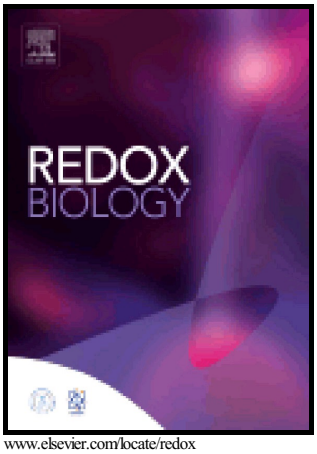

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Cardiomyocyte hypertrophy induced by Endonuclease G deficiency requires reactive oxygen radicals accumulation and is inhibitable by the micropeptide humanin

Natividad Blasco[a], Yolanda Cámara[b], Estefanía Núñez[c], Aida Beà[a], Gisel Barés[a], Carles Forné[d], Marisol Ruíz-Meana[e], Cristina Girón[a], Ignasi Barba[e], Elena García-Arumí[b], David García-Dorado[e], Jesús Vázquez[c], Ramon Martí[b], Marta Llovera[a], Daniel Sanchis[a,*].

a. Cell Signaling and Apoptosis group, Universitat de Lleida - IRBLleida, Lleida, Spain. b. Research Group on Neuromuscular and Mitochondrial Diseases, Vall d'Hebron Research Institute, Universitat Autònoma de Barcelona and CIBERER, Barcelona, Spain. c. Cardiovascular Proteomics group, Spanish National Center for Cardiovascular Research (CNIC) and CIBERCV Madrid, Spain. d. Biostatistics Unit, IRBLleida, Universitat de Lleida, Lleida, Spain. e. Cardiovascular Diseases Research Group, VHIR and CIBERCV, Barcelona, Spain.

*Corresponding author: Daniel Sanchis. Universitat de Lleida – IRBLLEIDA. Biomedicina-I Av. Rovira Roure, 80. 25190 Lleida. SPAIN. Email: daniel.sanchis@cmb.udl.cat.

Abstract

The *endonuclease G* gene (*Endog*), which codes for a mitochondrial nuclease, was identified as a determinant of cardiac hypertrophy. How ENDOG controls cardiomyocyte growth is still unknown. Thus, we aimed at finding the link between ENDOG activity and cardiomyocyte growth. *Endog* deficiency induced reactive oxygen species (ROS) accumulation and abnormal growth in neonatal rodent cardiomyocytes, altering the AKT-GSK3β and Class-II histone deacethylases (HDAC) signal transduction pathways. These effects were blocked by ROS scavengers. Lack of ENDOG reduced mitochondrial DNA (mtDNA) replication independently of ROS accumulation. Because mtDNA encodes several subunits of the mitochondrial electron transport chain, whose activity is an important source of cellular ROS, we investigated whether *Endog* deficiency compromised the expression and activity of the respiratory chain complexes but found no changes in these parameters nor in ATP content. MtDNA also codes for humanin, a micropeptide with possible metabolic functions. Nanomolar concentrations of synthetic humanin restored normal ROS levels and cell size in *Endog*-deficient cardiomyocytes. These results support the involvement of redox signaling in the control of cardiomyocyte growth by ENDOG and suggest a pathway relating mtDNA content to the regulation of cell growth probably

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